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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/405,046	09/27/1999	THOMAS MEADE	A-58634-6/RF	9059

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EXAMINER
JONES, DAMERON

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 03/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/405,046	MEADE ET AL.	
	Examiner	Art Unit	
	D. L. Jones	1616	

-- The MAILING DATE of this communicati n appears on the cover sheet with the corresp ndence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002 and 18 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

ACKNOWLEDGMENTS

1. The Examiner acknowledges Paper No. 22, filed 11/25/02, wherein the specification was amended; claims 12, 16, and 17 were canceled; claims 22, 30, 32, and 33 were amended; and claims 42-48 were added.

Note: Claims 22-48 are pending.

2. The Examiner acknowledges receipt of the acceptable terminal disclaimer filed 11/25/02, Paper No. 24.

3. The Examiner acknowledges Paper No. 23, filed 12/18/02, wherein a revised declaration was submitted.

RESPONSE TO APPLICANT'S AMENDMENT/ARGUMENTS

4. The Applicant's arguments filed 11/25/02 (Paper Nos. 22 and 24) to the rejection of claims made by the Examiner under 35 USC 103 and/or double patenting have been fully considered and deemed persuasive as it relates to the double patenting rejection. Therefore, the double patenting rejection is WITHDRAWN because Applicant has filed a terminal disclaimer.

In addition, the 103 rejection over claims 12, 16, and 17 are WITHDRAWN because Applicant has canceled those claims.

NEW GROUNDS OF REJECTION

112 Rejections

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 30-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30 and 42, lines 6-7 and 5-6, respectively: The claim as written is ambiguous because it is unclear what Applicant intends by the phrase 'such that the rapid exchange of water in at least one coordination site is said agent is increased'. In particular, 'rapid' is a relative term. Applicant is respectfully requested to the clarify the claim in order that one may readily ascertain what is being claimed. Likewise, since claims 31-48 depend on independent claims 30 and 42, one cannot readily ascertain what is encompassed by Applicant's claims.

Claim 32: The claim is ambiguous because it does not contain a period. Thus, it is unclear whether Applicant intended to add additional text or not. Please correct.

Claim 42, line 9: The claim is ambiguous because it is unclear what Applicant intends by the phrase 'therapeutic effect is elicited'. What therapeutic effect is Applicant referring to?

Claims 32-40: The claims as written are confusing because a dependent claim must refer to a preceding claim. Hence, claim 32 should not read on claim 42.

Likewise, the claims which depend upon claim 32 are confusing for the same reasons disclosed above.

102 Rejection

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 22-24, 28, and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Piwnica-Worms (US Patent No. 6,348,185).

Piwnica-Worms discloses a membrane permeant peptide complex useful for medical, diagnostic, and pharmaceutical purposes (see entire document, especially, abstract). In addition, Piwnica-Worms discloses (1) possible sequences for the cell membrane permeant peptide (column 13, lines 17-50); and (2) linker moieties (column 16, lines 11-68 and column 17, lines 1-26). (3) Functional linkers may be conjugated to the peptides. Possible linkers include protease-reactive or protease-specific sequences (e.g., caspase or sequences recognized by interleukin-1 beta), metalloproteases, and lysosomal proteases (e.g., cathespsins, HIV proteases) [column 17, line 22 through column 18, line18; columns 51-52, claims 8-11]. (4) One embodiment of Piwnica-

Worms is directed to a complex comprising a peptide, a protease specific moiety, a chelate, and a metal (column 18, lines 32-40). (5) In column 19, lines 17-26, it is disclosed that a metal-chelate complex (e.g., Gd-DTPA) comprising a relaxivity metal allows the T1 relaxivity to be detected within cells and tissues of living subjects using the appropriate T1 weighted pulse sequences by clinical magnetic resonance imaging devices. The appropriate magnetic resonance device can be operated to detect proton relaxivity changes in bodily water induced by relaxivity complex (column 19, lines 22-27) (6) Pharmacologically active substances may be conjugated to the complexes. Possible substances include proteases (column 20, lines 10-13). (7) Drugs and prodrugs may be designed that would enable selective delivery and retention of bioactive agents and therapeutic/biologic enhancers for therapy. Possible targeting agents include interleukins (column 20, lines 29-35). (8) The linker functionally may include any motif that may be acted on by a specific intracellular agent such as an enzyme. Possible linker functionalities include protease specific sequences (column 20, lines 41-54). Also, Piwnica-Worms disclose that protease sequences are particularly useful as they have the ability to amplify an image, radiotherapeutic, diagnostic, or therapeutic effect through enzymatic action on the conjugate complex which increases the intracellular concentration of a cleaved and subsequently trapped metal-chelate or other cargo molecule (column 12, lines 56-68). (9) Possible ligands useful with the invention of Piwnica-Worms include DTPA and DOTA (column 21, lines 58-62; column 52, claim 13). (10) Suitable relaxivity metals for generating magnetic resonance images include gadolinium. The ligands which coordinated the magnetic resonance

relaxivity metals may be readily incorporated into the peptide complexes by methods known in the art (columns 22-23, bridging paragraph). (11) A preferred embodiment disclosed by Piwnica-Worms is the coupling of DOTA to the peptide conjugate and using gadolinium as the magnetic resonance relaxivity metal (column 23, lines 44-47).

Thus, both Applicant and Piwnica-Worms disclose a substituted DOTA agent capable of being radiolabeled with gadolinium and conjugated to a peptide through a linker moiety.

103 Rejections

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 22, 25-27, and 30-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Piwnica-Worms (US Patent No. 6,348,185).

Piwnica-Worms fails to disclose other possible protease that may be used with their invention. In addition, the reference fails to specifically stated that the complex is used in a method wherein it is activatible in the subject. Also, Piwnica-Worms does not specifically state that their complexes undergo rapid exchange of water.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use an unlimited number of proteases because the cited

reference does not exclude any proteases that are not useful with their invention. Furthermore, Piwnica-Worms disclose that any functional linker with the intracellular component that confers target cell specificity to a peptide complex may be utilized (column 17, lines 19-32).

It would have been obvious to one of ordinary skill in the art at the time the invention was made that the magnetic resonance agent is activatible because Piwnica-Worms discloses that (a) a functional linker may be used that confers biological properties to the complex that makes it useful for imaging, diagnostics, or therapy. In addition, the cited prior art discloses that protease sequences are particularly useful because they result in amplification of an imaging, radiotherapeutic, diagnostic, or therapeutic effect through enzymatic action on the conjugate complex, thereby increasing the intracellular concentration of a cleaved and subsequently trapped metal-chelate or other cargo molecule (column 12, lines 56-68). Hence, the skilled practitioner would recognize that the complex is activatible.

It would have been obvious to a skilled practitioner in the art that the complexes of Piwnica-Worms are capable of rapidly releasing water because, the cited prior art (see column 19, lines 17-27), discloses that a skilled artisan in the art can readily operate the appropriate magnetic resonance imaging device to detect proton relaxivity changes in bodily water induced by relaxivity changes in bodily water induced by relaxivity complexes. Thus, a skilled practitioner is would be motivated to modify the water release to obtain the desired effect(s) (e.g., image results). Also, it should be

noted that claim 20 of Piwnica-Worms disclose that the relaxivity metal is monitored within the subject.

Furthermore, it is noted that a skilled practitioner in the art would recognize that the complex is activatible using any standard dictionary, e.g., Webster's Dictionary because a protease is any enzyme acts upon a peptide bond that results in splitting or hydrolyzing of that bond. Hence, any agent that is used for imaging that targets a specific location and generates an image has been 'activated'.

11. Claims 22 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gries et al (US Patent No. 5,648,063).

Gries et al disclose compositions comprising a chelate complex for magnetic resonance imaging. The complexes comprise one or more elements having atomic numbers 21-29, 42, 44, or 57-83 (see entire document, especially, abstract; column 3, lines 49-61; column 5, lines 24-43). Possible biomolecules which may be conjugated to the complexes include peptides and antibodies (column 4, lines 26-32). Conjugation may occur via a carboxyl group of t the complexing acid or by a CH2 group on a protein or peptide (column 4, lines 39-43). In column 23, Example 59, a solution of a gadolinium complex with DOTA and a monoclonal antibody is disclosed. While, Gries et al disclose a complex comprising a DOTA substituted with gadolinium and an antibody, the reference fails to disclose a complex comprising a DOTA substituted with gadolinium and a peptide.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Gries et al by replacing the monoclonal antibody with another targeting agent such as a peptide because, in column 4, lines 26-32, it is disclose that possible biomolecules which maybe be conjugated to the complexes of Gries et al include antibodies and peptides. Furthermore, it is noted that a skilled practitioner in the art would recognize using any standard dictionary, e.g., Webster's Dictionary that a protease is any enzyme acts upon a peptide bond that results in splitting or hydrolyzing of that bond. Hence, any agent that is used for imaging that targets a specific location and generates an image has been 'activated'.

12. Claims 22-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gries et al (US Patent No. 5,648,063) in view of Piwnica-Worms (US Patent No. 6,348,185).

Gries et al (see discussion above) fail to specifically state that a protease may be used with their invention and that rapid exchange of water occurs. Also, as noted above, Gries et al does not specifically state that their complex is activatible.

Piwnica-Worms (see discussion above).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Gries et al using the teachings of Piwnica-Worms and generate a substituted DOTA comprising gadolinium and a peptide that interacts with a protease because Piwnica-Worms discloses that various proteases may be used with their invention that encompasses substituted DOTA complexes. Also,

it is noted that Piwnica-Worms does not exclude any proteases that are not useful with their invention.

It would have been obvious to one of ordinary skill in the art at the time the invention was made that the magnetic resonance agent is activatible because Piwnica-Worms discloses that (a) a functional linker may be used that confers biological properties to the complex that makes it useful for imaging, diagnostics, or therapy. In addition, the cited prior art discloses that protease sequences are particularly useful because they result in amplification of an imaging, radiotherapeutic, diagnostic, or therapeutic effect through enzymatic action on the conjugate complex, thereby increasing the intracellular concentration of a cleaved and subsequently trapped metal-chelate or other cargo molecule (column 12, lines 56-68). Furthermore, it is noted that a skilled practitioner in the art would recognize using any standard dictionary, e.g., Webster's Dictionary that a protease is any enzyme acts upon a peptide bond that results in splitting or hydrolyzing of that bond. Hence, any agent that is used for imaging that targets a specific location and generates an image has been 'activated'.

It would have been obvious to a skilled practitioner in the art that the complexes are capable of rapidly releasing water because, the cited prior art (see Piwnica-Worms, column 19, lines 17-27), discloses that a skilled artisan in the art can readily operate the appropriate magnetic resonance imaging device to detect proton relaxivity changes in bodily water induced by relaxivity changes in bodily water induced by relaxivity complexes. Thus, a skilled practitioner is would be motivated to modify the water release to obtain the desired effect(s) (e.g., image results). Also, it should be noted that

claim 20 of Piwnica-Worms disclose that the relaxivity metal is monitored within the subject.

Since both Gries et al and Piwnica-Worms disclose substituted DOTA complexes capable of being complexed to gadolinium and a biomolecule, the references may be considered to within the same field of endeavor. Hence, the references are combinable.

COMMENTS/NOTES

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri. (alternate Mon.), 6:45 a.m. - 4:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose' Dees can be reached on (703) 308- 4628. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

D. L. Jones
Primary Examiner
Art Unit 1616

March 10, 2003